Claims

1. A synthetic mutein of a biologically active protein which protein has at least one cysteine residue that is free to form a disulfide link and is nonessential to said biological activity, said mutein having at least one of said cysteine residues deleted or replaced by another amino acid.

2. The synthetic mutein of claim 1 wherein there is only one of said cysteine residues.

3. The synthetic mutein of claim 1 wherein said cysteine residues are replaced by serine, threonine, glycine, alanine, valine, leucine, isoleucine, histidine, tyrosine, phenylalanine, tryptophan, or methionine.

4. The synthetic mutein of claim 1 wherein said cysteine residues are replaced by serine or threonine.

5. The synthetic mutein of claim 1 wherein the mutein is unglycosylated.

6. The synthetic mutein of claim 1 wherein the protein is IFN-ß, IL-2, lymphotoxin, colony stimulating factor-1, or IFN-αl.

7. The synthetic mutein of claim 1 wherein the protein is IFN-ß, the cysteine residue is at position 17 of IFN-ß, and the cysteine residue is replaced by a serine residue.

8. The synthetic mutein of claim 7 wherein the mutein is unglycosylated.

9. The synthetic mutein of claim 6 wherein the protein is IL-2, the cysteine residue is at position 125 of IL-2, and the cysteine residue is replaced by serine.

10. The synthetic mutein of claim 9 wherein the mutein is unglycosylated.

11. A structural gene having a DNA sequence that encodes the synthetic mutein of claim 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10.

12. An expression vector that includes the structural gene of claim 11 in a position that permits expression thereof.

13. A host cell or organism transformed with the expression vector of claim 12 and progeny thereof.

14. E.coli transformed with the expression vector of claim 12 and progeny thereof.

15. A process for making a synthetic mutein comprising culturing the host or progeny of claim 13 and harvesting the synthetic mutein from the culture.

16. A method of preventing a protein having at least one cysteine residue that is free to form a disulfide link from forming said link comprising mutationally altering the protein by deleting the

cysteine residue or replacing the cysteine residue with another amino acid.

17. The method of claim 16 wherein the protein is biologically active and the cysteine is not essential to said biological activity.

18. The method of claim 16 or 17 wherein the cysteine residue is replaced with serine or threonine.

19. A method for making the gene of claim 11 comprising:

(a) hybridizing single-stranded DNA comprising a strand of a structural gene that encodes said protein with a mutant oligonucleotide primer that is complementary to a region of said strand that includes the codon for said cysteine residue or the antisense triplet paired with said codon, as the case may be, except for a mismatch with said codon or said antisense triplet which mismatch defines a deletion of the codon or a triplet that codes for said other amino acid;

(b) extending the primer with DNA polymerase to form a mutational heteroduplex; and

(c) replicating said mutational heteroduplex.

20. The method of claim 19 wherein the mismatch defines a triplet that codes for serine or threonine.

21. The method of claim 19 wherein the single-stranded DNA is a single-stranded phage that

includes said strand and the mutational heteroduplex of step (b) is converted to closed circular heteroduplex.

22. The method of claim 19 wherein said replicating is effected by transforming a competent bacterial host with the closed circular heteroduplex and culturing the resulting transformants.

23. The method of claim 19 including the additional steps of isolating progeny of the mutant strand of the heteroduplex, isolating DNA from said progeny, and isolating said gene from the DNA from said progeny.

24. The method of claim 19, 20, 21, 22 or 23 wherein the protein is human IFN-ß, the cysteine residue is at position 17, and the mismatch defines a codon for serine.

25. The method of claim 24 wherein the strand is the antisense strand of IFN-ß and the mutant oligonucleotide primer is GCAATTTTCAGAGTCAG.

26. The method of claim 19, 20, 21, 22, or 23 wherein the protein is human IL-2, the cystein residue is at position 125 and the mismatch defines a codon that codes for serine.

27. An oligonucletide for use in making the structural gene of claim 11 by oligonucleotide-directed mutagenesis having a nucleotide sequence that is complementary to a region of the strand of the structural gene that includes the codon for the

cysteine residue or the antisense triplet paired with said codon, as the case may be, except for a mismatch with said codon that defines a deletion of the codon or a triplet that codes for said other amino acid.

28. A therapeutic composition having IFN-ß activity comprising a therapeutically effective amount of the synthetic mutein of claim 7 or 8 admixed with a pharmaceutically acceptable carrier medium.

29. A therapeutic composition having IL-2 activity comprising a therapeutically effective amount of the synthetic mutein of claim 9 or 10 admixed with a pharmaceutically acceptable carrier medium.

30. Plasmid pSY2501.

31. Bacteria transformed with plasmid pSY2501, and progeny thereof.

32. The bacteria of claim 31 wherein the bacteria are E.coli.

33. IFN-ß$_{ser17}$.

34. Plasmid pLW46.

35. Plasmid pLW55.

36. Bacteria transformed with plasmid pLW46 or plasmid pLW55, and progeny thereof.

37. The bacteria of claim 35 wherein the bacteria are E.coli.

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38. des-ala $^{\wedge}$IL-2$_{ser125}$.

39. Ala-IL-2$_{ser125}$.

40. A method of regulating cell growth in a patient comprising administering to said patient a cell growth regulating amount of the compound of claim 33.

41. A method of treating a patient for a viral disease comprising administering to said patient a viral disease inhibiting amount of the compound of claim 33.

42. A method of stimulating natural killer cell activity in a patient comprising administering to said patient a natural killer cell stimulating amount of the compound of claim 33.

add B'

add C2